UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/720,177	11/25/2003	Jun Nakamura	US-110	6388

38108 7590 11/24/2010

CERMAK NAKAJIMA LLP
ACS LLC
127 S. Peyton Street
Suite 210
ALEXANDRIA, VA 22314

EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
11/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

cgoode@cermaknakajima.com
ip@cermaknakajima.com
scermak@cermaknakajima.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JUN NAKAMURA and KAYO AKIYAMA

Appeal 2010-002880
Application 10/720,177
Technology Center 1600

Before CAROL A. SPIEGEL, LORA M. GREEN, and
MELANIE L. McCOLLUM, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge.*

DECISION ON APPEAL[1]

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's rejection of claims 1, 4, 5, 12-16, and 18-21. Claims 8-11 are also pending, but stand withdrawn from consideration. (App. Br. 3.) We have jurisdiction under 35 U.S.C. § 6(b).

---

[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

STATEMENT OF THE CASE

Claim 1 is the only independent claim on appeal and reads as follows:

1. An isolated coryneform bacterium having L-glutamine-producing ability, wherein said bacterium has been modified by disrupting or mutating a glutaminase gene on the chromosome so that the glutaminase activity of the bacterium is reduced to 0.1 U/mg of cellular protein or less, wherein said glutaminase gene is selected from the group consisting of:

a) a DNA comprising the DNA sequence of SEQ ID NO: 1, and

b) a DNA which is able to hybridize with the DNA of SEQ ID NO: 1 under stringent conditions of 1 X SSC, 0.1% SDS, at 60°C, and is 95% or more homologous to SEQ ID NO: 1.

The following grounds of rejection are before us on appeal:

I. Claims 1, 4, 5, 12-16, and 18-21 stand rejected under 35 U.S.C. § 112, second paragraph.

II. Claims 1, 4, 5, 12-16, 18, 19, and 21 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

III. Claims 1, 4, 5, 12-16, and 18-21 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

IV. Claims 1, 4, 5, 13-16, and 19-21 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Nakamura,[2] Pompejus,[3] Jakoby,[4] Nakagawa,[5] and Durán.[6]

---

[2] Nakamura, EP 1 229 121 A2, published August 7, 2002.
[3] Pompejus, WO 01/00843 A2, published January 4, 2001.
[4] Jakoby et al., *Isolation of the Corynebacterium glutamicum glnA gene encoding glutamine synthetase I*, 154 FEMS MICROBIOLOGY LETTERS 81-88 (1997).

We reverse rejections I, II, and III, but affirm rejection IV.

ISSUE I

Has the Examiner set forth a prima facie case that the use of the term "homology" renders the claims on appeal indefinite?

FINDINGS OF FACT

FF1 The Examiner's statement of the rejection may be found at pages 3-13 of the Examiner's Answer.

FF2 Specifically, the Examiner finds that claims "1, 5 and 16 . . . are indefinite in the recitation of '95% or more homologous to SEQ ID NO: X.'" (Ans. 3.)

FF3 According to the Examiner, as the Specification

> does not provide the specific parameters/methods intended in the calculation of sequence homology (e.g., PAM matrices), one of skill in the art cannot determine the scope of the term "95% homologous" because a percent sequence homology value for a set of sequences is variable depending on the parameters used in the calculation and Appellant has not set forth the intended method/parameters for that calculation.

(*Id.* at 3-4.)

FF4 The Examiner then set forth two different alignments using different parameters (*id.* at 4-15), finding that one set of parameters finds that the

---

[5] Nakagawa, EP 1 108 790 B1, published June 20, 2001.
[6] Durán et al., *The role of glutaminase in Rhizobium etli: studies with a new mutant*, 141 MICROBIOLOGY 2883-2889 (1995).

sequences are 95.4% homologous, while another set of parameters finds that the sequences are 96.1% homologous (*id.* at 37).

PRINCIPLES OF LAW

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). Claims are in compliance with 35 U.S.C. § 112, second paragraph, if "the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986).

ANALYSIS

Appellants argue that "standardized and well-practiced methods for determining homology between sequences [are] known to those of skill in the art," such as through the use of the BLAST program. (App. Br. 8.)

We agree with Appellants. The results shown by the Examiner demonstrate that the use of different parameters may result in a conclusion that two sequences may be 95.4% homologous or 96.1% homologous. Given that the difference is only 0.7% and given that the use of alignment programs such as BLAST is well known and routine with the art, the skilled artisan would reasonably understand the metes and bounds of the claim limitation "95% or more homologous to SEQ ID NO: 1."

CONCLUSION OF LAW

We conclude that the Examiner has not set forth a prima facie case that the use of the term "homology" renders the claims on appeal indefinite. We thus reverse the rejection of claims 1, 4, 5, 12-16, and 18-21 under 35 U.S.C. § 112, second paragraph.

ISSUE II

Has the Examiner established a prima facie case that the Specification fails to describe the claims on appeal within the meaning of 35 U.S.C. § 112, first paragraph?

FINDINGS OF FACT

FF5 The Examiner's statement of the rejection may be found at pages 13-15 of the Answer.

FF6 The Examiner notes that the "claims require a precise reduction in glutaminase activity to a specific level of glutaminase activity (0.1 U/mg or 0.01 U/mg) and a precise ratio of glutamine synthetase activity to glutaminase activity (2:1) obtained by any means." (Ans. 14, original emphasis.)

FF7 The Examiner finds that neither the Specification nor the prior art provides an "adequate description of the genus of methods by which one could achieve the required activity levels." (*Id.*)

FF8 The Examiner finds further that as "the claims require a precise level of reduction in enzymatic activity and/or a precise ratio of enzymatic activities," that the Specification

> should provide some description as to how one of skill in the art should mutate the recited glutaminase genes such that those mutations would result in that precise level of enzymatic activity reduction in any coryneform bacterium as recited . . . . [as well as] adequate description as to the modifications that can be made to a coryneform bacterium as recited such that one could achieve the desired ratio.

(*Id.*)

FF9 The Examiner also finds, citing Witkowski[7] for the proposition that "even a single conservative substitution can result in enzymatic activity changes," that the Specification and prior art do not "provide a structure/function correlation for glutaminases or glutamine synthetases that would allow one of skill in the art to envision the structural modifications required in the recited genes to obtain the desired reduction in glutaminase activity, or the desired ratio of glutaminase to glutamine synthetase activity." (*Id.* at 15.)

PRINCIPLES OF LAW

"The burden of showing that the claimed invention is not described in the application rests on the PTO in the first instance." *In re Edwards*, 568 F.2d 1349, 1354 (CCPA 1978).

> [T]he determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the

---

[7] Witkowski et al., *Conversion of a β-Ketoacyl Synthase to a Malonyl Decarboxylase by Replacement of the Active-Site Cysteine with Glutamine*, 38 BIOCHEMISTRY 11643-11650 (1999).

> predictability of the aspect at issue, and other considerations appropriate to the subject matter.

Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005).

ANALYSIS

Appellants argue that a "precise" reduction in glutaminase activity, or a precise ratio of glutaminase to glutamine synthetase activity is not required by the claims, but that the claims set an upper limit and encompass activities below those limits. (App. Br. 10-11.)

We agree with Appellants that the Examiner appears to be interpreting the claims to require a "precise" reduction in glutaminase activity or a "precise" ratio of glutaminase to glutamine synthetase activity. The claims, however, do not require a precise glutaminase activity or a precise ratio of glutaminase to glutamine synthetase activity, but set an upper limit, and anything that falls below that upper limit is encompassed by the claim.

CONCLUSION OF LAW

We conclude that the Examiner has not established a prima facie case that the Specification fails to describe the claims on appeal within the meaning of 35 U.S.C. § 112, first paragraph. We are thus compelled to reverse the rejection of claims 1, 4, 5, 12-16, 18, 19, and 21 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

ISSUE III

Has the Examiner established a prima facie case that the Specification fails to enable the full scope of the claims on appeal?

FINDINGS OF FACT

FF10 The Examiner's statement of the rejection may be found at pages 15-20 of the Answer.

FF11 Specifically, according to the Examiner, the Specification,

> while being enabling for a C. *glutamicum* cell, wherein said cell has been modified to reduce the endogenous glutaminase activity and to increase glutamine synthetase activity, wherein the reduction in glutaminase activity is due to an inactivating deletion in the endogenous glutaminase gene of said C. *glutamicum* cell, wherein the endogenous glutaminase gene comprises SEQ ID NO: 1 prior to the introduction of the deletion, and the increase in glutamine synthase activity is due to (i) an increase in the copy number of the C. *glutamicum* glnA gene of SEQ ID NO: 3, or (ii) an increase in expression of the *C. glutamicum* glnA gene of SEQ ID NO: 3 by placing said gene under the control of a heterologous promoter, does not reasonably provide enablement for (1) a coryneform bacterium modified to reduce glutaminase activity to less than 0.1 U/mg protein or 0.01 U/mg protein in said bacterium by mutating any region of a glutaminase gene comprising SEQ ID NO: 1 or a structural homolog thereof, (2) the coryneform bacterium of (1) further modified in any way to modulate any glutamine synthetase activity such that the recited ratio (2 to 1) of glutamine synthetase activity to glutaminase activity is achieved, or (3) the coryneform bacterium of (1) further modified by increasing the expression of a glutamine synthetase gene which is a structural homolog of the nucleic acid of SEQ ID NO: 3, wherein said increase in expression is obtained by increasing the copy number of the glutamine synthetase gene or by replacing the endogenous promoter of the glutamine synthetase gene with a stronger promoter.

(Ans. 15-16.)

FF12 The Examiner finds that the teachings of the Specification are not commensurate in scope with the claimed subject matter as the Specification does not teach:

> (A) the mutations which would result in (1) a coryneform bacterium to have a glutaminase activity which is 0.1/0.01 U/mg cellular protein or less, or (2) a coryneform bacterium to have the recited glutaminase activity and the recited ratio of glutaminase to glutamine synthetase activity, (B) the structure of any glutamine synthetase gene and mutations required to modulate the expression of said gene so that the recited ratio of glutaminase to glutamine synthetase is obtained, and (C) the structural features required in any structural variant of the polynucleotide of SEQ ID NO: 3 such that it can encode a protein having glutamine synthetase activity.

(*Id.* at 17.)

FF13 As with the written description rejection, the Examiner also finds that the Specification lacks any disclosure of mutations that would lead to the precise reduction in glutaminase activity, as well as those mutations that would result in the precise glutaminase to glutamine synthetase activity. (*Id.* at 18.)

FF14 The Examiner also reiterates that neither the Specification nor the art provides a structure/function correlation, "such that one of skill in the art can envision the structure of any nucleic acid encoding a glutamine synthetase," or "such that one of skill in the art would know which structural modifications are required to obtain the desired effect in glutaminase and glutamine synthetase activity." (*Id.*)

FF15 The Examiner also finds:

> While methods of generating or isolating variants of a polynucleotide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for any number of polynucleotides and determine which ones encode glutamine synthetases. In addition, it was not routine in the art to screen by trial and error for (1) essentially an infinite number of mutations in either the regulatory region of a gene or in the coding region of a gene to determine which ones result in reduced glutaminase activity or enhanced glutamine synthetase activity, as recited in the claims, (2) all possible enhancers of glutamine synthetase activity such as chemicals and the products of other genes, or (3) all possible transcription enhancers of genes encoding glutamine synthetases such as chemicals and the products of other genes.

(*Id.* at 19.)

PRINCIPLES OF LAW

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F.2d 220, 223 (CCPA 1971) (emphasis added).

"[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id.* at 224.

ANALYSIS

Appellants reiterate their argument that a "precise" reduction in glutaminase activity, or a precise ratio of glutaminase to glutamine synthetase activity is not required by the claims, but that the claims set an upper limit and encompass activities below those limits. (App. Br. 12-13.)

We agree with Appellants. As noted above with respect to the written description requirement, the claims do not require a precise glutaminase activity or a precise ratio of glutaminase to glutamine synthetase activity, but set an upper limit, and anything that falls below that upper limit is encompassed by the claim. In addition, the Specification teaches different methods of reducing glutaminase [GLS] activity (*see* Spec. 9-10), and as also noted by the Examiner in the obviousness rejection, "inactivation of genes by introducing deletions/insertions if the sequence of the target gene is known is well known and widely practiced in the art" (Ans. 34.) Thus, it would have been well within the level of skill of the art to disrupt glutaminase. In addition, Nakamura teaches coryneform bacterium having increased glutamine synthetase activity. Moreover, the Specification teaches assays for determining glutaminase and glutamine synthetase activity (*see* Specification, Examples, pp. 20-33). Moreover, there is no requirement that the Specification enable all possible ways of achieving the claimed subject matter, which the Examiner is apparently requiring. (*See, e.g.*, FF15.)

CONCLUSION OF LAW

We conclude that the Examiner has not established a prima facie case that the Specification fails to enable the full scope of the claims on appeal.

We are thus compelled to reverse the rejection of claims 1, 4, 5, 12-16, and 18-21 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

ISSUE IV

Has the Examiner established by a preponderance of the evidence that the combination of references cited renders obvious the coryneform bacterium of claim 1?

FINDINGS OF FACT

FF16 The Examiner's statement of the rejection may be found at pages 21-35 of the Answer. As Appellants have not argued the claims separately, we focus our analysis on claim 1, and claims 4, 5, 13-16, and 19-21 stand or fall with that claim. 37 C.F.R. § 41.37(c)(1)(vii).

FF17 The Examiner cites Nakamura for teaching a method of "producing L-glutamine by fermentation of an L-glutamine producing *C. glutamicum* cell," wherein the cell has been modified to increase the copy number of the gene encoding glutamine synthetase. (Ans. 21.)

FF18 Specifically, Nakamura:

> relates to an L-glutamine producing bacterium belonging to coryneform bacteria and a method for producing L-glutamine. L-Glutamine is an industrially useful amino acid as an ingredient of seasonings, liver function promoting agents, amino acid transfusions, comprehensive amino acid preparations, and so forth.

(Nakamura, ¶1.)

FF19 The Examiner notes that Nakamura does not teach "a method for producing L-glutamine wherein glutaminase activity is reduced." (Ans. 21.)

FF20 The Examiner cites Durán for teaching that "glutaminase degrades glutamine to yield glutamate and ammonium." (*Id.*)

FF21 The Examiner finds that Durán teaches a *Rhizobium* mutant, "wherein the chromosomal glutaminase gene is disrupted by Tn5 mutagenesis," and that the mutants have increased levels of glutamine as compared to wild-type. (*Id.* at 21-22.)

FF22 The Examiner thus finds that Durán "clearly teach[es] that by reducing glutaminase activity, there is an increase in glutamine levels." (*Id.* at 44.)

FF23 Specifically, Durán teaches:

> Since the low glutaminase activity observed in the LM16 mutant should result in impairment of the catabolism of glutamine to glutamate, we measured the intracellular glutamine and glutamate pools in LM16 under different growth conditions. In comparison with the wild-type strain, LMl6 showed a 53-fold higher glutamine content and a threefold lower glutamate content when grown on glutamine as nitrogen and carbon source, a sixfold higher glutamine and a twofold lower glutamate content when grown on glutamine plus succinate, a twofold higher glutamine and a threefold lower glutamate content when grown on ammonium plus succinate and a twofold higher glutamine and similar glutamate content when grown on PY-rich medium (Table 1). This indicates that the inability of LMl6 to grow on glutamine as nitrogen and carbon source is not due to the lack of transport of this amino acid.

(Durán, p. 2886 (first column).) Durán thus concludes that the metabolic block is in the degradation of glutamine. (*Id.* at 2887, first column.)

FF24 The Examiner notes that Durán does not teach "a *C. glutamicum* or coryneform bacterium deficient in glutaminase." (Ans. 22.)

FF25 The Examiner cites Jakoby for teaching a glutamine synthetase gene from *C. glutamicum* that has 99.1% identity to SEQ ID NO: 3. (*Id.*)

FF26 The Examiner further cites Pompejus for teaching a glutaminase gene from *C. glutamicum* that has 99.1% identity to nucleotides 827-1687 of SEQ ID NO: 1. (*Id.* at 25.) The Examiner cites Nakagawa for teaching the remaining structure of the glutaminase gene of Pompejus. (*Id.* at 28-29.)

FF27 The Examiner concludes that it would have been obvious to disrupt or modify the glutaminase gene in *C. glutamicum* because Nakamura teaches a *C. glutamicum* for the production of glutamine, and Durán teaches that disruption of glutaminase results in higher levels of glutamine. (*Id.* at 34.)

PRINCIPLES OF LAW

A rejection for obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The proper question to ask is whether a person of ordinary skill in the art, facing the wide range of needs created by developments in the field of endeavor, would have seen a benefit to combining the prior art teachings. *KSR*, 550 U.S. at 424; *see also In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (the desirability of the combination may arise from nature of the problem, teachings of references, or the ordinary knowledge of those skilled in the art). In addition,

> [w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable

> solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance, the fact that a combination was obvious to try might show it was obvious under §103.

KSR, 550 U.S. at 421.

ANALYSIS

Appellants argue that "Duran only teaches uptake of glutamine added to the medium by the bacterial cells, and does not show production of glutamine by the LM16 strain in the culture medium." (App. Br. 15.) According to Appellants, "it is known that glutamine is synthesized from glutamate and ammonium via the catalytic effect of glutamine synthetase," and thus the ordinary artisan "would know that the production of glutamine decreases when the intracellular glutamate concentration decreases." (*Id.*) Appellants further assert that from Figure 3 of Durán, the ordinary artisan would understand that "glutaminase is clearly not involved, or involved very minimally, in the degradation of glutamine." (*Id.* at 16.)

Appellants' arguments have been carefully considered, but are not found to be convincing. As found by the Examiner, Nakamura teaches a method of using a *C. glutamicum* to produce L-glutamine. (*See* FF17.) Nakamura teaches that the L-glutamine can then be obtained from the medium. (Nakamura, ¶54.) Durán teaches that glutaminase is involved in the breakdown of L-glutamine to yield glutamate and ammonium. (*See* FF20.) Thus, we agree with the Examiner that it would have been obvious to the ordinary artisan to suppress glutaminase activity by disrupting or

mutating the gene for glutaminase on the chromosome in order to suppress the breakdown of L-glutamine to glutamate and ammonium.

As to Appellants' argument that glutamine is synthesized from glutamate and ammonium via the catalytic effect of glutamine synthetase, as taught by Nakamura, many carbon sources are known, such as "glucose, glycerol, fructose, sucrose, maltose, mannose, galactose, starch hydrosolysate and molasses, and organic acids such as acetic acid and citric acid, and alcohols such as ethanol." (Nakamura, ¶56.) In addition, the disruption of the glutaminase gene would merely prevent the desired product, L-glutamine, from being degraded to glutamate and ammonium. Finally, as to Appellants' argument that Figure 3 of Durán demonstrates that glutaminase is not involved, or involved very minimally, in the degradation of glutamine, this is contrary to the specific teachings of Durán, as Durán clearly teaches that "glutamine is also degraded by a glutaminase which catalyses its hydrolytic deamidation to yield glutamate and ammonium." (Durán, p. 2884, first column.)

Appellants further assert that Durán uses a rhizobial strain, asserting that "[i]t is known that the rizobial [sic] strains use nitrogen assimilation similar to that used and studied in plants," and that "later review papers which describe the nitrogen metabolism of other types of bacteria such as the Corynebacterium and *E. coli*, do not describe the glutaminase as described in Duran." (App. Br. 16.) Appellants also argue that in the *Rhizobium* bacterium of Durán, that when glutamine is used as the sole carbon source, an enzyme called GOGAT would not work, whereas when glucose is added to the medium, that enzyme would have a greater

contribution to the degradation of glutamine. (*Id.* at 17.) Thus, Appellants assert, Durán does not "teach or suggest an increased glutamine level in a glutaminase-deficient bacterium when glucose is present in the medium," and as such, actually teaches away from the claimed invention. (*Id.*)

Appellants' arguments are again not convincing. While Appellants argue that later reviews apparently distinguish the glutaminase of Corynebacterium and *E. Coli* from that of the rhizobial strain of Durán, Appellants have not provided those review papers, and arguments of counsel cannot take the place of evidence in the record. *In re Scarbrough*, 500 F.2d 560, 566 (CCPA 1974). Similarly, Appellants have not provided any evidence to support their arguments based on the role of the GOGAT enzyme, such that the ordinary artisan would not expect that disruption of the glutaminase gene would not inhibit breakdown of the desired product, L-glutamine.

Finally, our mandate is to give claims their broadest reasonable interpretation. *In re American Academy Of Science Tech Center*, 367 F.3d 1359, 1364 (Fed. Cir. 2004). Claim 1 is drawn to "[a]n isolated coryneform bacterium having L-glutamine-producing ability," thus any coryneform bacterium that has the ability to produce L-glutamine, as long as it meets the remaining limitations of the claim, would be encompassed by claim 1.

CONCLUSION OF LAW

We conclude that the Examiner established by a preponderance of the evidence that the combination of references cited renders obvious the coryneform bacterium of claim 1. We thus affirm the rejection of claims 1,

4, 5, 13-16, and 19-21 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Nakamura, Pompejus, Jakoby, Nakagawa, and Durán.

SUMMARY

We reverse the rejections under 35 U.S.C. § 112 of claims 1, 4, 5, 12-16, and 18-21, but affirm the obviousness rejection of claims 1, 4, 5, 13-16, and 19-21.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED-IN-PART

cdc

SPIEGEL, *Administrative Patent Judge.* Concurring-in-part and Dissenting-in-part.

I agree with the decision of the majority of this panel to reverse the ground of rejection under 35 U.S.C. § 112, second paragraph (definiteness), and to affirm the obviousness rejection under 35 U.S.C. § 103(a). However, I respectfully disagree with respect to the grounds of rejection under 35 U.S.C. § 112, first paragraph (written description and enablement), which I would affirm. I focus my attention on claims 1 and 14.

A. Representative Claims

Claim 1, the sole independent claim on appeal, and claim 14 are representative and read as follows (App. Br. 20-21).

> 1. An isolated coryneform bacterium having L-glutamine-producing ability, wherein said bacterium has been modified by disrupting or mutating a glutaminase gene on the chromosome so that the glutaminase activity of the bacterium is reduced to 0.1 U/mg of cellular protein or less, wherein said glutaminase gene is selected from the group consisting of:
>
> a) a DNA comprising the DNA sequence of SEQ ID NO:1, and
>
> b) a DNA which is able to hybridize with the DNA of SEQ ID NO: 1 under stringent conditions of 1 X SSC, 0.1% SDS, at 60°C, and is 95% or more homologous to SEQ ID NO: 1.
>
> 14. The bacterium of claim 1, wherein the glutaminase activity of the bacterium is reduced to 0.01 U/mg of cellular protein or less.

A. Written Description

1. Positions of Appellants and the Examiner

The Examiner agrees with Appellants "that disruption of the glutaminase gene … would result in no glutaminase activity (0 U/mg), and 0 U/mg protein is a species of the genus of levels of [reduced] glutaminase activity recited" (Ans. 39). However, the Examiner correctly points out that the claims encompass not only bacteria lacking glutaminase activity, but also bacteria mutated to achieve a specified reduced level of glutaminase activity of 0.1 U/mg cellular protein (claim 1) or 0.01 U/mg cellular protein (claim 14) (*id.*). According to the Examiner, since these levels of glutaminase activity "are the main embodiments of the genus of glutaminase activity levels recited, one of skill in the art would expect, at a minimum, that the specification would adequately describe those embodiments which are considered representative of the genus" (*id.*).

Appellants argue that claim 1 "does not require one to achieve exactly [a glutaminase activity of] exactly 0.1 U/mg, … only that the [glutaminase] gene is disrupted or mutated so that the level falls below this activity number" (App. Br. 10-11). According to Appellants, "disruption and/or mutation of genes are well-known procedures in the art, and the teachings of the specification combined with these well-known methods clearly demonstrate that the claimed invention is adequately described" (*id.* at 11).

Appellants further argue that, based on the submitted amino acid alignment of various glutaminases (Exhibit A), one of ordinary skill in the art "would clearly recognize which regions are important for the enzymatic activities of the proteins … and would be able to reduce the activities of the proteins by introducing amino acid mutations at such regions" (*id.*).

According to the Examiner, Appellants' amino acid sequence alignment data is unpersuasive because conserved amino acid regions may be evolutionary artifacts which are not necessarily related to enzyme activity and, therefore, do not provide guidance/suggestion as to the effect of making a particular modification on enzymatic activity levels absent additional structure/function correlation information (Ans. 39-40). The Examiner cites Seffernick[8] and Witkowski (*see* n.7 *supra*) as evidence that two proteins having 98% sequence identity can have two different functions, i.e., catalyze two different reactions, and that even a single conservative can result in enzymatic activity changes, respectively (Ans. 15, 40-41). Thus, the Examiner maintains that, absent some structure/function correlation or some guidance as to which mutations are required to obtain the desired reduction in glutaminase activity, one of skill in the art cannot reasonably conclude that the claimed invention is adequately described in the Specification (*id.* at 15).

These are not new arguments. The Examiner and Appellants have maintained substantially the same positions throughout prosecution of the instant Application. For example, on page 3 of the Pre-Appeal Brief Request for Review filed June 17, 2008, Appellants argued that based on

> the alignment of the protein sequences of glutaminase (gls) (Exhibit A …), one of ordinary skill in the art would clearly recognize which regions are important for the enzymatic activities of the proteins, and would be able to reduce the

---

[8] Seffernick et al., *Melamine Deaminase and Atrazine Chlorohydrolase: 98 Percent Identical but Functionally Different*, 183 JOURNAL OF BACTERIOLOGY 2405-2410 (2001) ("Seffernick").

> activities of the proteins by introducing amino acid mutations at such regions, and hence the claims are fully and adequately described. Furthermore, one of ordinary skill in the art would be able to readily ascertain expression regulatory sequence of the recited glutaminase gene on the chromosome of a coryneform bacterium based on the sequence information for glutaminase genes, and would be able to mutate or disrupt the expression regulatory sequence of the recited glutaminase gene. That is, one of ordinary skill in the art would be able to obtain a coryneform bacterium in which gluatminase activity is reduced to 0.1U/mg of cellular protein or less, by mutating or disrupting the recited glutaminase gene … and/or by mutating or disrupting expression regulatory sequence of the recited glutaminase gene, based on the known sequence information for glutaminase genes, the teaching of the specification, and the knowledge and level of skill in this art. No undue experimentation is required to determine such information, and the invention is fully and adequately described ….

Similarly, on pages 6-7 of the Office action mailed October 16, 2008, prior to mailing of the Answer, the Examiner stated that

> as previously indicated, the written description issue … is the fact that the claims require a precise reduction in glutaminase activity to a specific level of glutaminase activity (0.1 U/mg or 0.01 U/mg) …obtained by any means. … However, in view of the fact that the claims require a precise level of reduction in enzymatic activity, the specification should provide some description as to how one of skill in the art should mutate the recited glutaminase genes such that those mutations would result in that precise level of enzymatic activity

> reduction in any coryneform bacterium as recited, or how should one [sic] modulate expression of the recited genes to obtain the desired level of enzymatic activity. …
>
> With regard to the alignments …, it is unclear … how one could look at the conserved regions in the alignments and determine which modifications would result in the desired effect if (1) there is no structure/function correlation that would provide one of skill in the art with some suggestion as to the effect of making a particular modification on function, (2) the art as previously discussed [i.e., Seffernick and Witkowski] teaches the unpredictability of determining a priori the effect of structural changes on a protein's function based solely on structural similarity, and (3) … there is no indication as to how these conserved regions are related to the enzymatic activity required by the claims.

Thus, the Examiner's position as to coryneform bacteria having reduced glutaminase activity (which is required by all of the claims on appeal) is two-fold. First, the claims expressly recite bacteria having two ranges of reduced activity extending from no enzyme activity to a precise upper limit -- "0.1 U/mg cellular protein or less" (claim 1) and "0.01 U/mg cellular protein or less" (claim 14) -- but the Specification only describes bacteria with inactivated glutaminase activity. Second, the Specification only describes reducing glutaminase activity by totally disrupting the gene which encodes the glutaminase, while the claimed invention (but for claim 20) encompasses any method for reducing glutaminase activity, including mutating the gene at an unknown position(s) to produce a modified protein

of desired activity from 0 U/mg cellular protein to 0.01 U/mg cellular protein (claim 14) or to 0.1 U/mg cellular protein (claim 1).

Appellants' position, on the other hand, is that the claims do not require bacteria having the *exact* upper limit of reduced glutaminase activity recited in the claims. Instead, the claims simply require bacteria having reduced glutaminase activity less than the "precise" upper limit recited in the claims. According to Appellants, the alignments of glutaminase amino acid sequences (Exhibit A), the teachings of the Specification, and the ordinary level of skill in the art adequately describe the claimed invention.

2. Issue

At issue is whether the Specification describes the invention of claims 1 and 14 as required by the first paragraph of § 112.

3. Legal principles

> To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* ...([Fed. Cir.] 1997); *In re Gosteli*, ... (Fed. Cir. 1989). . . . Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, ...

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1566 (Fed. Cir. 1997). "The description requirement of the patent statute

requires a description of an invention, not an indication of a result that one might achieve if one made that invention." *Id.* at 1568.

> To satisfy the written description requirement in a case of a chemical or biotechnological genus, more than a statement of the genus is normally required. One must show that one had possession, as described in the application, of sufficient species to show that he or she invented and disclosed the totality of the genus.

Carnegie Mellon University v. Hoffmann-La Roche Inc., 541 F.3d 1115, 1126 (Fed. Cir. 2008).

4. Additional findings of fact

FF28 SEQ ID NO: 1 of the Specification is the gene encoding the glutaminase of *Brevibacterium flavum* strain ATCC 14067 (Specification 8).

FF 29 The Specification describes a modified strain of *B. flavum* strain ATCC 14067 wherein the gene encoding glutaminase has been disrupted (Specification 23-27).

FF30 The Examiner found that neither the Specification nor the prior art provides a structure/function correlation for glutaminases. (Ans. 15).

5. Analysis

Claim 1 broadly recites a genus of isolated coryneform bacteria which have been modified such that their glutaminase activity is reduced to a level of 0.1 U/mg cellular protein or less, wherein the gene encoding the glutaminase protein comprises the DNA of SEQ ID NO: 1 or a DNA at least 95% homologous thereto under hybridization conditions recited in claim 1.

SEQ ID NO: 1 is nucleotide sequence encoding the glutaminase of *Brevibacterium flavum* strain ATCC 14067 (FF 28). Thus, claim 1 encompasses modified coryneform bacteria having glutaminase activities between 0.1 U/mg cellular protein and no glutaminase activity. In other words, contrary to Appellants' position, claim 1 does not just encompass bacteria which have been modified to having a reduced level of glutaminase activity vis-à-vis the parent strains, but also bacteria which have been modified to specified levels of glutaminase activity, i.e., 0.1 U/mg cellular protein and 0.01 U/mg cellular protein as expressly recited in claims 1 and 14.

The Specification describes a modified coryneform bacterium at one end of the recited range, i.e., no glutaminase activity due to the disruption of the gene encoding the protein (FF 29). However, the Specification does not describe a modified coryneform bacterium with glutaminase activity at the upper end of glutaminase activity expressly recited in claims 1 and 14. Thus, Appellants have not shown that they had possession, as described in the Specification, of sufficient species to show that they invented and disclosed the totality of the genus recited in claim 1 (or in claim 14). *Carnegie Mellon University v. Hoffmann-La Roche*, 541 F.3d at 1126.

6. Conclusion

The Specification does not describe the totality of the genus of modified bacteria recited in claims 1 and 14 as required by the first paragraph of § 112. Contrary to Appellants' argument that claim 1 only requires that the glutaminase gene is "disrupted or mutated so that the level falls below this activity number" as argued by Appellants (App. Br. 10-11),

for example, the genus of claim 1 clearly includes a bacteria modified to achieve a glutaminase activity of exactly 0.1 U/mg cellular protein as correctly interpreted by the Examiner.

B. Enablement

1, Positions of Appellants and the Examiner

The Examiner acknowledges that the Specification enables complete inactivation of the gene encoding glutaminase (Ans. 15). However, according to the Examiner,

> [t]he enablement provided [by the Specification] is not commensurate in scope with the claims due to the lack of information as to (A) the mutations which would result in (1) a coryneform bacterium to have a glutaminase activity which is 0.1/0.01 U/mg cellular protein or less, … [Ans. 17.]

Appellants argue that

> one of ordinary skill in the art would be able to obtain a coryneform bacterium in which glutaminase activity is reduced to *0.1 U/mg of cellular protein or any level below this activity level*, by mutating or disrupting the recited glutaminase gene on the chromosome of a coryneform bacterium and/or by mutating or disrupting expression regulatory sequence of the recited glutaminase gene, based on the known sequence information for glutaminase genes, the teaching of the specification, and the knowledge and level of skill in this art. No undue experimentation is required to determine such information, particularly in view of the knowledge in the prior art regarding the sequences. [App. Br. 13-14, original emphasis.]

Again, these are not new arguments. The Examiner and Appellants have maintained substantially the same positions throughout most of the prosecution of the instant Application. For example, on page 3 of the Pre-Appeal Brief Request for Review filed June 17, 2008, Appellants argue

> one of ordinary skill in the art would be able to obtain a coryneform bacterium in which glutaminase activity is reduced to 0.1 U/mg of cellular protein or less, by mutating or disrupting the recited glutaminase gene on the chromosome of a coryneform bacterium and/or by mutating or disrupting expression regulatory sequence of the recited glutaminase gene, based on the known sequence information for glutaminase genes, the teaching of the specification, and the knowledge and level of skill in the art. No undue experimentation is required to determine such information, ….

Similarly, on page 10 of the Office action mailed October 16, 2008, prior to mailing of the Answer, the Examiner maintained that

> (1) there is no structure/function correlation that would provide one of skill in the art with some suggestion as to the effect of making a particular modification on function, (2) the art as previously discussed clearly teaches the unpredictability of determining a priori the effect of structural changes on a protein's function based solely on structural similarity, and (3) the conserved regions shown in the alignment are the regions which are conserved <u>among the proteins used in the alignment</u> and there is no indication as to how these conserved regions are related to the enzymatic activity required by the claims. Thus, contrary to Applicant's assertion, alignments such as those provided by Applicant would not provide

> the necessary structure/function correlation which would allow one of skill in the art to determine a priori which modifications are most likely to result in the desired effect. Therefore, to enable the entire scope of the claims, one of skill in the art would have to test an infinite number of mutations to determine which ones result in the desired enzymatic activity ….(original emphasis).

2. Issue

At issue is whether the Specification enables the full scope of claims 1 and 14 as required by the first paragraph of § 112.

3. Legal principles

"[T]o be enabling, the specification … must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). "That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) (original emphasis). Some experimentation, even if a considerable amount, is not "undue" if, for example the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

4. Additional findings of fact

FF31 According to the Specification, glutaminase activity may be reduced by treating bacteria with UV radiation or a mutagenzing agent and/or by gene disruption and then screening for bacteria with the desired level of residual glutaminase activity (Specification 9-10).

5. Analysis

Claims 1 and 14 encompass coryneform bacteria modified by any type of mutation to a glutaminase gene to reduce glutaminase activity to a specific level of 0.1 or 0.01 U/mg cellular protein, respectively. The Specification generally describes mutating bacteria by UV irradiation, with a mutagenizing agent, and by gene disruption (FF 31). One of skill in the art would reasonably expect that disrupting the glutaminase gene would result in expression of an inactive glutaminase protein, if any glutaminase protein at all. Furthermore, one of skill in the art would reasonably expect that mutagenesis of the glutaminase gene of a bacterium would encode a glutaminase with reduced activity vis-à-vis that of the unmodified parent bacterium. However, this is the precise point at which the Examiner and Appellants part company. Appellants emphasize that claims 1 and 14 encompass modified bacteria having less than 0.1 and 0.01 U glutaminase activity/mg cellular protein and, therefore, general knowledge in the art, including a nucleotide sequence a glutaminase gene from a coryneform bacterium and well-known methods of gene mutagenesis suffice to enable a skilled artisan to make and use the subject matter of claims 1 and 14. The Examiner, however, correctly emphasizes that claims 1 and 14 include modified bacteria having precisely 0.1 and 0.01 U glutaminase activity/mg cellular protein, not merely any reduction in glutaminase activity vis-à-vis the unmodified bacteria.

Given the breadth of claims 1 and 14, including bacteria having the expressly recited upper level of glutaminase activity, the evidence of unpredictability submitted by the Examiner, and the lack of any specific

structure/function guidance in the Specification, I agree with the Examiner that it would require undue experimentation to modify a coryneform bacterium to obtain the precise level of glutaminase activity encompassed by the scope of claims 1 and 14. In other words, mutating a bacterium and then screening for mutants with a desired level of residual glutaminase activity is insufficient to enable full scope of claims 1 and 14 absent undue experimentation.

6. Conclusion

The Specification does not enable the full scope modified bacteria recited in claims 1 and 14 as required by the first paragraph of § 112 because it would require undue experimentation to make bacteria modified to achieve a glutaminase activity of exactly 0.1 or 0.01 U/mg cellular protein as included in the scope of claims 1 and 14.

CERMAK NAKAJIMA LLP
ACS LLC
127 S. PEYTON STREET
SUITE 210
ALEXANDRIA, VA 22314